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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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09/320,609 05/26/99 WILUSZ

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EXAMINER

HM12/1002

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MORAN, M

ART UNIT

PAPER NUMBER

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/320,609	WILUSZ ET AL.	
	Examiner	Art Unit	
	Morjorie Moran	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on _____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,2,4-6 and 9-55 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,2,4-6 and 9-55 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|---------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) <u>10</u> . | 6) <input checked="" type="checkbox"/> Other: <i>detailed action and attach</i> . |

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The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. All rejections and objections not repeated below are hereby withdrawn.

Information Disclosure Statement

The IDS filed 4/27/01 has been fully considered.

Claim Objections

Claims 10, 14, 25, 36, and 37 are objected to because of the following informalities: In claims 14, 25, and 36, the term --an-- should be inserted before "unlabeled" and the term --a-- should be inserted before "labeled", both in line 2 of each claim. In claim 37, the term "is" before "selected" in line 2 should be deleted. For clarity, the examiner recommends that the following phrase be inserted after "polyadenylate" in claim 10, line 3: --, wherein said material is--.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 30-32 and 43-45 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods to identify an agent which modulates the stability of a target RNA sequence by modulating the activity of an AU rich element (ARE) binding

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protein, does not reasonably provide enablement for similar methods wherein the agent modulates the activity of a C-rich element binding protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. This is a SCOPE OF ENABLEMENT rejection.

The claims are enabled for methods to identify an agent which modulates the stability of a target RNA sequence by modulating the activity of an AU rich element (ARE) binding protein because both the specification and the prior art teach how to do so; however, neither the prior art nor the specification teach identification of an agent which modulates RNA stability by modulating C-rich element binding proteins. The specification discloses on pages 5 and 8 that regulated RNA turnover may be C-rich element mediated turnover and that RNA stability modifiers include C-rich element binding proteins. However, the originally filed specification does not identify any particular C-rich elements which are involved in RNA turnover or stability. The specification discloses on pages 37-38 that Elav-family proteins, such as HuR, bind to AREs and are involved in modulating RNA stability/degradation. The prior art is replete with examples of proteins which bind ARE and are known to be involved in modulation of RNA stability/degradation (see e.g. NAKAMAKI et al. (IDS ref.); ZHANG et al. (IDS ref.), and NAKAGAWA et al. (IDS ref.)). As both the specification and prior art teach ARE binding proteins known to be involved in modulation of RNA stability/degradation, the claims are enabled for methods wherein an agent modulates the activity of ARE binding proteins. However, as set forth above, the originally filed specification fails to teach any C-rich element binding proteins, particularly any which are involved in modulation of RNA stability/degradation. The prior art does not teach that C-rich elements are involved in modulation of RNA stability, nor does the prior art teach C-rich element binding proteins which are known to modulate RNA

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stability/degradation. As neither the prior art nor the instant specification teach C-rich element binding proteins which are involved in modulation of RNA deadenylation and degradation, the claims are not enabled for method of identifying agents which modulation RNA deadenylation and degradation and modulate the activity of C-rich element binding proteins.

Claims 48-50 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This is an ENABLEMENT rejection.

The specification does not teach that agents which modulate the stability of a target RNA sequence are necessarily agents which are involved in cell growth or differentiation, cellular transformation, or intervenes in immune dysregulation. An agent which modulates the stability of an mRNA which encodes an ion-channel protein expressed in mature cells, for example, is not an RNA directly involved in growth or differentiation or transformation of that cell. One skilled in the art would need to first identify an RNA which is itself involved in cell growth and differentiation, or is itself involved in cellular transformation, or would need to identify an RNA which encodes a protein or peptide which is involved in cell growth and differentiation or is involved in cellular transformation. After identifying such an RNA, one skilled in the art would then need to determine whether modulation of the stability of that RNA affects the identified cell growth and differentiation or transformation. One skilled in the art would need to develop a method for identifying the RNA and/or protein, and would need to develop a method to identify whether or not stability of the RNA CAN be affected, then need to develop an assay to measure changes in stability of the RNA, and would need to tailor the method such that changes in stability measured in the method are correlated to changes in cell growth and differentiation or

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transformation. The immune system is known in the art to be very complex, with many factors contributing to regulation or dysregulation thereof. It would require a great deal of experimentation by one skilled in the art to determine what part of the immune system is "regulated" by any given RNA, or if it is "regulated" by a single RNA or by a groups of RNA's before one skilled in the art could determine if an RNA is involved in dysregulation. The prior art does not teach such methods. The specification merely recites the same limitations as are recited in the claims, but does not teach any method steps for carrying out the claimed methods. Given the many methods which must be developed, and the many variables in those methods which must be performed to determine if an agent which modulates RNA stability is also an agent which modulates cell growth and differentiation, or cellular transformation, or immune dysfunction, in a mammal, and the lack of teaching by either the specification or the prior art for how to carry out the claimed methods, it would require undue experimentation by one skilled in the art to determine how to identify an agent which modulates cell growth and differentiation, transformation, or immune dysfunction by determining the ability of the agent to modulate RNA stability. For these reasons, claims 48-50 are not enabled.

Claims 31 and 44 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a LACK OF WRITTEN DESCRIPTION rejection.

Claims 31 and 44 each recites "tristetrapolin" in line 3. This protein is disclosed on pages 2, 7-8, and 20 of the instant specification, but is not identified other than as a member of the ELAV family. The other proteins recited in claims 31 and 44 are known in the art by the

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names/acronyms recited in the claims. However, a search of multiple databases for a protein named "tristetrapolin" reveals no protein known in the art by that name. As "tristetrapolin" is not identified, characterized or otherwise described by the prior art or in the originally filed specification, claims 31 and 44 are rejected for lack of written description.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 9-11, 15-17, 21-50 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 9-11 appear to recite method steps but are dependent from claim 1, which is directed to a system (device). A method of making is not generally a limitation of a product. In the instant case, the system of claim 1 is limited to comprise an extract which is depleted of polyadenylate (polyA) binding proteins. The method of depletion apparently recited in claims 9-11 does not further limit the device itself. As it is unclear what limitation of the device of claim 1 is intended by the method steps recited in claims 9-11, claims 9-11 are indefinite.

Claims 10 and 25 recite "antibodies to proteins that bind polyadenylate, polyadenylate, and the combination thereof", each in lines 4-5. It is unclear if applicant intends (a) antibodies to proteins which bind polyA, antibodies to polyA, and antibodies to a combination of polyA and proteins which bind polyA, or intends (b) antibodies to proteins which bind polyA, antibodies to polyA, and a mixture of antibodies to polyA and antibodies to proteins which bind polyA, or intends (c) polyA, antibodies to proteins which bind polyA, and a mixture of polyA and antibodies to proteins which bind polyA. As the language of the claims renders unclear what

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limitation is intended, the claims are indefinite. The examiner recommends rewriting the claims to make both the members of the group and the "combination" intended clear.

Claims 10 and 25 each recite "the combination" in line 4. There is no antecedent basis for this term in the claims, therefore the claims are indefinite. This rejection may be overcome by replacing "the" with --a-- before "combination" in each claim.

Claims 14, 25, and 36 each recite "the combination" in lines 2-3. There is no antecedent basis for this term in the claims, therefore the claims are indefinite. This rejection may be overcome by replacing "the" with --a-- before "combination" in each claim.

Claims 15, 26, and 37 each recite "a ligand" in line 3. It is unclear what molecule the labeled moiety is intended to be a ligand for, therefore the metes and bounds of the claim are unclear and the claims are indefinite.

Claims 16-17, 22-23, and 34-35 further limit the system of claim 1 to comprise an exogenously added nucleoside triphosphate, specifically ATP. Claim 1 recites that the system comprises a source of ATP, therefore it is unclear if applicant intends that the system comprise ATP and another, exogenously added, nucleoside triphosphate, or if applicant intends to limit the ATP of the system of claim 1 to be exogenous, therefore the claims are indefinite. Applicant should note that if claims 16, 22, and 34 are amended to limit the ATP of claim 1 to be an exogenously added nucleoside triphosphate, then claims 17, 23, and 35 will not be further limiting of claims 16, 22, and 34, respectively.

Claim 21 recites "said turnover" in step (D). There is no antecedent basis for this term in the claims, therefore use of the term renders the claim indefinite. For purposes of applying the prior art, the claim will be interpreted as if "turnover" were --deadenylation and degradation--.

Claims 31 and 44 recite "a member of the ELAV family;" followed by a list of proteins. It is unclear if applicant intends the members of the ELAV family to be limited to the proteins

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following the semicolon or merely intends the list of proteins to be exemplary members of the ELAV family, therefore the claims are indefinite. If applicant intends the proteins to be exemplary, then the claims are further indefinite. See MPEP § 2173.05(d).

Claims 32 and 45 depend from claims 31 and 44, respectively, and recite different proteins than are recited in each parent claim. It is unclear what limitation of the proteins recited in parent claims 31 and 44 is intended in claims 32 and 45, therefore claims 32 and 45 are indefinite.

Claims 31 and 44 each recites "tristetrapolin" in line 3. As this protein is not identified, characterized or otherwise described by either the prior art or the specification (see above), it is unclear what limitation is intended by this term, therefore the claims are indefinite.

Claim 47 recites "providing the system of claim 1 in the presence of a nucleoside triphosphate" in step (A). The system of claim 1 comprises an ATP source, therefore it is unclear what applicant intends by "in the presence of a nucleoside triphosphate". It is noted that "in the presence of" does not limit the nucleoside triphosphate to be added to the system of claim 1. It is therefore unclear (a) whether applicant intends the system of claim 1 to comprise a nucleoside triphosphate in addition to or different from the ATP of claim 1, and (b) whether applicant intends the nucleoside triphosphate to be added to the system of claim 1, therefore the claim is indefinite.

Claim 51 recites "isolating" a molecule "as capable of participating in the deadenylation or degradation of RNA..." One may identify or characterize a molecule "as capable or participating in..." a reaction, or may isolate a molecule which has been identified as one which IS capable of participating in a reaction, but does not generally isolate a molecule "as capable of participating in" a reaction. The language of the claims makes the limitation intended by "isolating" a molecule unclear, therefore the claim is indefinite.

Claim 51 recites "said target RNA" in step (C). There is no antecedent basis for this term in the claim, therefore the claim is indefinite.

Claim 55 recites a method of identifying an agent capable of modifying degradation of a target RNA, then recites a methods step of monitoring degradation of the target RNA, but does not recite any actual identification step. In the absence of an identification step, it is unclear whether the method actually identifies an agent capable of modulating RNA degradation, therefore the claim is indefinite.

Claim Rejections - 35 USC § 103

Claims 1, 5-6, 9-17, 21-29, 33-42, 46-47, and 51-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of BERNSTEIN et al. (Mol. Cell. Biol. (2/1989) vol. 9 (2), pages 659-670), LEVY et al. (J. Biol. Chem. (2/2/1996) vol. 271 (5), pages 2746-2753), and LEVY et al. (J. Biol. Chem. (3/13/1998) vol. 273 (11), pages 6417-6423), and SHAPIRO (Biochemistry (1969) vol. 8 (2), pages 659-670).

Applicant's arguments with respect to the claims have been considered but are moot in view of the new ground(s) of rejection. Applicant's arguments with regard to BERNSTEIN are addressed below.

Claim 1 recites an in-vitro system comprising a cytoplasmic extract supernatant from a 100,000xg, 1 hour centrifugation, wherein the cytoplasmic extract is isolated from eukaryotic cells or tissues and is depleted of polyadenylate binding proteins (PABP), a source of ATP, and an exogenous target RNA sequence. Claim 2 limits the intended use of the system of claim 1. Claim 5 limits the cell extract of claim 1 to one from cells comprising foreign nucleic acid. Claim 6 limits the cell extract of claim 1 to one from cells which are uninfected, infected, transfected, or transiently transfected. Claims 9-11 limit the depletion of PABPs to particular method steps.

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Claim 53 recites a kit comprising directions for use, unidentified reagents, and a cytoplasmic extract supernatant from a 100,000xg, 1 hour centrifugation which is depleted of PABPs. Claim 54 limits the kit to further comprise nucleotide triphosphates, a reaction enhancer, a target RNA sequence, or a combination of these. Claim 21 recites a method of identifying an agent capable of modulation the in-vivo stability of a target RNA sequence comprising providing the system of claim 1, introducing the (test) agent into the system, determining the "extent" of deadenylation and degradation of the target sequence, and identifying the (test) agent as one able to modulate stability if it can modulate the "extent" of deadenylation and degradation of the target RNA.

Claim 47 recites a similar method wherein the system of claim 1 is provided "in the presence of a nucleotide triphosphate". As it is unclear what limitation is intended by this phrase, and as the system of claim 1 comprises ATP, for purposes of applying the prior art, claim 47 is interpreted to be reciting the same method as claim 21. Claim 33 recites a similar method to claim 21, with the addition of a stability modifier to the system. Claim 46 recite a method of identifying an agent capable of modulating regulated deadenylation of a target RNA and recites the same method steps as claim 21. Claim 51 recites a method of identifying, characterizing or isolating an endogenous molecule "suspected of participating" in deadenylation and degradation, or regulation thereof, of RNA comprising providing the system of claim 1, introducing an endogenous molecule into the system, monitoring the stability of target RNA in the system, and identifying or characterizing the endogenous molecule as one able to modulate stability if it can modulate the "extent" of deadenylation and degradation of the target RNA, or isolating the molecule if it is so characterized or identified. Claim 52 limits the endogenous molecule to be a protein or RNA. Claim 55 recites a method of identifying an agent capable of modulating degradation of a target RNA sequence in the absence of deadenylation comprising providing a cell extract in the presence of a nucleotide triphosphate, introducing the agent into

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the cell extract, and monitoring degradation of the target RNA in the extract. Claims 16-17, 22-23, and 34-35 limit the ATP to be exogenously added. Claim 24 limits the agent identified in the method of claim 21 to be an RNA stability modifying molecule. Claims 12-13 limit the target RNA sequence. Claims 14, 25, and 36 limit the target RNA to be labeled or unlabeled or a mixture. Claims 15, 26, and 37 limit the label. Claims 27 and 38 limits the determination of deadenylation and degradation in the method of claims 21 and 33, respectively, to be determination of degradation of labeled RNA. Claim 28 limits the modulation of stability of claim 21 to be an increase in stability. Claim 29 limits the modulation of stability of claim 21 to be a decrease in stability. Claim 39 limits the stability modifier to one which increases RNA stability. Claim 40 limits the agent to one which decreases stability of the RNA stabilized by the stability modifier. Claim 41 limits the stability modifier of claim 33 to be one which decreases stability of the target RNA. Claim 42 limits the agent of claim 41 to one which increases the stability of target RNA which was decreased by the stability modifier.

BERNSTEIN teaches a "system" and method and makes obvious a kit for identifying agents capable of modulating deadenylation and degradation of target RNA, as previously set forth and maintained. BERNSTEIN teaches that a cellular extract is subjected to a high salt incubation, and centrifuged wherein both the supernatant and "ribosomal salt wash fraction" (RSW) are harvested (p. 660, left column). BERNSTEIN further teaches that PABPs are expressed in the cytoplasm of cells (p. 661). As previously set forth, BERNSTEIN teaches that his extracts may be depleted of PABPs by various means, including addition of polyA and extraction over a polyA-Sepharose column (pp. 661-662). BERNSTEIN teaches that his PABPs, polyA, and antibodies to PABPs are all stability modifiers for his target RNA, and teaches that addition of one can "counteract" the change in stability of another (pp. 662-662). BERNSTEIN does not teach a 100,000xg, 1 hour centrifugation, or exogenously added ATP.

SHAPIRO teaches that ATP and UTP stimulate deadenylating enzyme activity (abstract). SHAPIRO does not teach a 100,000xg, 1 hour centrifugation.

LEVY (1996) teaches a method of measuring RNA degradation using an S100 cytoplasmic extract wherein a homogenate from a high salt incubation is centrifuged at 100,000xg for one hour (p. 2747), and teaches identification of mRNA binding proteins which modulate degradation (p. 2748, right column).

It would have been obvious to one of ordinary skill in the art at the time of invention to have used the S100 cytoplasmic extract of LEVY (1996) as the cell extract in the system and method of BERNSTEIN where the motivation would have been to use an in-vitro system which faithfully recapitulates regulated expression and degradation of RNA, as taught by LEVY (1998, p. 6421). One skilled in the art would reasonably have expected success in using the S100 extract as the cellular extract in the system and method of BERNSTEIN because LEVY teaches that his S100 extract may be successfully used to measure RNA degradation and to identify agents which modulate that degradation, and BERNSTEIN teaches that either polysomes or a *soluble* high salt extract of polysomes (i.e. a supernatant) may be used in his system and method (p. 660). It also would have been obvious to one skilled in the art to add the ATP of SHAPIRO to the system and method of BERNSTEIN and LEVY where the motivation would have been to ensure and/or stimulate activity of deadenylation enzymes, as taught by SHAPIRO, wherein BERNSTEIN teaches that deadenylation is a critical step in degradation of polyA containing RNAs. One skilled in the art would reasonably have expected success in adding the exogenous ATP of SHAPIRO to the cell-free extracts in the system and method of BERNSTEIN and LEVY because BERNSTEIN teaches deadenylation in his method and SHAPIRO teaches that ATP successfully stimulates deadenylation. It would further have been obvious to have formulated the S100 extract, ATP, and target RNA sequence taught by LEVY,

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SHAPIRO, and BERNSTEIN into a kit with directions for use where the motivation would have been to facilitate use of the method made obvious by BERNSTEIN, LEVY, and SHAPIRO.

In response to the argument that BERNSTEIN does not teach use of a supernatant from a 100,000xg, 1 hour centrifugation, it is noted that the rejection set forth above is made over a combination of references wherein LEVY teaches a cytoplasmic S100 extract for use in RNA degradation assays. In response to the argument that BERNSTEIN discards his supernatant and uses only polysomes or *materials extracted from polysomes using high salt* (emphasis added by examiner), it is noted that BERNSTEIN does NOT teach discarding his supernatant but specifically teaches that both supernatant and an RSW fraction (pellet?) are harvested after a centrifugation step, and teaches that a soluble high salt extract of polysomes may be used in his system and method. As *soluble* components are usually those which do NOT precipitate in a centrifugation step, the examiner interprets BERNSTEIN's teaching of a soluble high salt extract to be the supernatant resulting from a high salt wash. LEVY teaches that his S100 extract is the supernatant from a high salt (1.5 M KCl) wash of a cytoplasmic extract. In addition, as set forth above, LEVY teaches that his S100 extract can be successfully used in methods to monitor RNA degradation and to identify agents which modulate said degradation, therefore it would have been obvious to have substituted the S100 extract of LEVY for the cell extract in the system and method of BERNSTEIN for the reasons set forth above. In response to the argument that the references previously cited do not address the mechanism of polyA removal, it is noted that no "mechanism" is recited in the claims. As previously set forth and maintained in previous office actions, BERNSTEIN teaches a method to "recapitulate" regulated deadenylation and degradation of RNA. Also, as set forth above, the S100 extract of LEVY is taught to be one which "recapitulates" regulated RNA expression and degradation.

Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over BERNSTEIN et al. (Mol. Cell. Biol. (2/1989) vol. 9 (2), pages 659-670), LEVY et al. (J. Biol. Chem. (2/2/1996) vol. 271 (5), pages 2746-2753), and LEVY et al. (J. Biol. Chem. (3/13/1998) vol. 273 (11), pages 6417-6423), and SHAPIRO (Biochemistry (1969) vol. 8 (2), pages 659-670) as applied to claim 1 above, and further in view of KRIKORIAN et al. (J. Virology (1/1991) vol. 65, pages 112-122).

Applicant's arguments with respect to claim 4 have been considered but are moot in view of the new ground(s) of rejection. Applicant argues that KRIKORIAN teaches use of a cell lysate and does not teach a centrifugation step. In response, applicant's attention is drawn to p. 113, end of the section titled "In vitro RNA degradation extracts" wherein KRIKORIAN teaches removal of nuclei from a HeLa cell extract by centrifugation and storage of supernatant on ice. KRIKORIAN specifically teaches use of these cytoplasmic supernatant in his degradation assays (last paragraph on page 113).

Claim 1 recites a system for identifying an agent capable of modulating regulated deadenylation and degradation of a target RNA sequence, as set forth above. Claim 4 limits the cytoplasmic cell extract to be from HeLa cells.

BERNSTEIN, LEVY, LEVY, and SHAPIRO make obvious a system and method for identifying an agent capable of modulating regulated deadenylation and degradation of a target RNA sequence, as set forth above. None of BERNSTEIN, LEVY, LEVY, or SHAPIRO teach a cytoplasmic cell extract from HeLa cells.

KRIKORIAN teaches a cytoplasmic cell extract from HeLa cells for use in an mRNA degradation assay (p. 113, right column).

It would have been obvious to one of ordinary skill in the art at the time of invention to have used the HeLa cells of KRIKORIAN to make the S100 cytoplasmic extract in the method of BERNSTEIN, LEVY, LEVY, and SHAPIRO where the motivation would have been to use a

mammalian cell line which is particularly suitable for the preparation of in vitro translation extract and thus provide a best initial approximation to a functional cytoplasm (i.e. in vivo conditions), as taught by KRIKORIAN (p. 114, right column).

Claims 2, 30-32, and 43-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over BERNSTEIN et al. (Mol. Cell. Biol. (2/1989) vol. 9 (2), pages 659-670), LEVY et al. (J. Biol. Chem. (2/2/1996) vol. 271 (5), pages 2746-2753), and LEVY et al. (J. Biol. Chem. (3/13/1998) vol. 273 (11), pages 6417-6423), and SHAPIRO (Biochemistry (1969) vol. 8 (2), pages 659-670) as applied to claims 1, 21, 33, and 41 above, and further in view of MYER et al. (EMBO (1997) vol. 16 (8), pages 2130-2139) and CHEN et al. (Mol. Cell. Biol. (10/1995) vol. 15 (10), pages 5777-5788).

Applicant's arguments with respect to claim 2, 30-32 and 43-45 have been considered but are moot in view of the new ground(s) of rejection.

The claims recite a system and methods of identifying an agent capable of modulating regulated deadenylation and degradation of a target RNA sequence, as set forth above. Claim 2 limits the regulated deadenylation and degradation to be that mediated by ARE's or C-rich elements. Claims 30 and 43 limit the agent of claim 21 to be one which modulates an ARE binding protein or a C-rich element binding protein. Claims 31-32 and 44-45 limit the ARE binding protein to specific proteins.

BERNSTEIN, LEVY, LEVY, and SHAPIRO make obvious a system and method for identifying an agent capable of modulating regulated deadenylation and degradation of a target RNA sequence, as set forth above. None of BERNSTEIN, LEVY, or SHAPIRO teach ARE binding proteins.

MYER teaches that HuR binds to AREs and destabilizes mRNA in in vitro assays (p. 2136). MYER also teaches that HuD, HuC, and Hel N1 are ARE binding proteins in the Elav family which may act similarly to HuR (p. 2136). MYER further teaches hnRNP A1 and C, AU-A, AU-B, and AU-C, which are known to bind AREs and are implicated in destabilization of mRNA (p. 2131, left column).

CHEN teaches that binding of U-rich-sequence (ARE) binding proteins to RNA are modified by agents which modify deadenylation of RNA (p. 5786).

It would have been obvious to one of ordinary skill in the art at the time of invention to identify agents which modify binding of the Elav-family proteins taught by MYER to an mRNA in the method made obvious by BERNSTEIN, LEVY, LEVY, and SHAPIRO where the motivation would have been to use an in vitro assay (protein binding) to predict the ability of agents to modify RNA stability in vivo, as taught by MYER (p. 2131, right column). One skilled in the art would reasonably have expected success in using the assay of BERNSTEIN, LEVY, LEVY, and SHAPIRO to identify agents which modulate regulated deadenylation and degradation by modulating the activity of an ARE binding protein because MYER teaches that ARE binding proteins are known to be involved in RNA stabilization and CHEN teaches that agents which modify deadenylation appear to also modify binding ARE binding proteins (p. 5786).

Claims 18-20 and 53 are rejected under 35 U.S.C. 103(a) as being unpatentable over BERNSTEIN et al. (Mol. Cell. Biol. (2/1989) vol. 9 (2), pages 659-670), LEVY et al. (J. Biol. Chem. (2/2/1996) vol. 271 (5), pages 2746-2753), and LEVY et al. (J. Biol. Chem. (3/13/1998) vol. 273 (11), pages 6417-6423), and SHAPIRO (Biochemistry (1969) vol. 8 (2), pages 659-670) as applied to claims 1 and 53 above, and further in view of FELLIG et al. (Arch. Biochem. Biophys. (1959) vol. 85, pages 313-316).

Applicant's arguments with respect to claims 18-20 and 53 have been considered but are moot in view of the new ground(s) of rejection.

The claims recite a system and kit for identifying an agent capable of modulating regulated deadenylation and degradation of a target RNA sequence, as set forth above. Claims 18-20 and 53 further limit the system and kit to comprise a reaction enhancer, specifically polyvinyl alcohol.

BERNSTEIN, LEVY, LEVY, and SHAPIRO make obvious a system and kit for identifying an agent capable of modulating regulated deadenylation and degradation of a target RNA sequence, as set forth above. None of BERNSTEIN, LEVY, LEVY, and SHAPIRO do not teach polyvinyl alcohol (PVA).

FELLIG teaches that anionic polymers, such as polyvinyl alcohol, inhibit ribonucleases (abstract).

It would have been obvious to of ordinary skill in the art at the time of invention to have added the PVA of FELLIG to the cytoplasmic cell extract in the system and kit of BERNSTEIN, LEVY, LEVY, and SHAPIRO where the motivation would have been to inhibit nonspecific degradation of the RNA in the extract by ribonucleases, as suggested by FELLIG's teaching that PVA inhibits ribonuclease and BERNSTEIN's teaching for addition of protease inhibitors in buffers in his method/system (p. 661).

Conclusion

Claims 1-2, 4-6, 9-55 are rejected; claims 10, 14, 25, 36, and 37 are objected to.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marjorie A. Moran whose telephone number is (703) 305-2363. The examiner can normally be reached on Monday to Friday, 7:30 am to 4 pm EST.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on (703) 308-4028. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4556 for regular communications and (703) 308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to a patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.



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